THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE

(Project Description)

Request to the Office of Naval Research for Renewal of

Contract NR 113-149
Serial 18249
Naonr 181-53

(83)

I. Background Information

Since July 1951 a project designed to develop a synthetic drug which would be as safe as codeine with respect to toxicity, antitussive activity, and addiction liability has been carried on within the National Institute of Mental Health Addiction Research Center, PHS Hospital, Lexington, Kentucky. This project has been financed in large part by funds from the Office of Naval Research and this description constitutes a request for renewal of the project for the period 1 July 1957 to 30 June 1958.

A synthetic substitute for codeine is badly needed since opium or morphine derived from opium constitute the only source of codeine. Unless a synthetic substitute for codeine is found the United States must continue to stockpile opium in order to provide adequate supplies of codeine for both the civilian and military populations in the event of war. The facilities of the NIMH Addiction Research Center are not sufficient to carry out this work, in addition to drug testing

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required for the evaluation of all new analgesics, unless additional funds are supplied by the Department of Defense.

2. Work Accomplished to Date

Previous work has been summarized in the annual progress reports sent to Capt. F. H. Quimby and Capt. T. K. Ruebush of the Physiology Branch, Office of Naval Research.

Two drugs have been developed which are promising potential substitutes for codeine for relief of cough. These drugs are (1) dextromethorphan, and (2) narcotine. Neither drug possesses any addiction liability and both have relatively low toxicity. The studies reported at the meeting of Committee on Drug Addiction and Narcotics of the National Research Council, in January 1957, continue to indicate that the drugs are as effective as codeine for relief of cough. It seems almost certain, therefore, that the antitussive phase of the problem has, in a sense, been solved.

Although the antitussive problem is no longer as pressing as it was, there are still no compounds available which are known to be as effective and safe as codeine for relief of mild grades of pain. More than 35 materials have now been screened for this purpose. The outstanding substance which has been developed is d-alpha-4-dimethylamino-1,2-diphenyl-3-methyl-4-propionoxybutane, or d-Propoxyphene. Preliminary

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but unconfirmed work indicates that this compound is as effective as codeine as an analgesic in clinical practice. Extensive work has shown that, although the compound possesses addictive potentialities, the overall addiction liability is considerably less than that of codeine. This drug, therefore, is quite promising, but final evaluation must wait completion of extensive clinical trial for relief of pain.

3. Need for Continuation of the Project

The chief need for continuation of the project is related to uncertainty concerning the analgesic potency of d-Propoxyphene. If clinical trials show that this drug is as effective as codeine then all aspects of our original problem would be completely solved. Since, however, we cannot be certain at this time that d-Propoxyphene will replace codeine in clinical use, it is still essential that the search for synthetic substitutes must be continued since the larger the number of compounds tested the greater the chance of finding completely adequate substitutes.

4. Work Proposed

During the period from 1 July 1957 to 30 June 1958 we propose to test the addictive properties of D-3-methoxy-N-phenethyl morphinan, D-3-hydroxy-N-phenethyl morphinen, Normorphine, Norcodeine, and N-allyldihydrohydroxy codeinone.

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In addition, studies of other substances referred by the Committee on Drug Addiction and Narcotics of the National Research Council will be carried on.

5. Methods

The methods to be used are the standard addiction liability testing methods of the NIMH Addiction Research Center. These methods are accepted as standard by the Committee on Drug Addiction and Narcotics and have been described in previous project descriptions, which should be consulted for details.

6. Evaluation of Data

The evaluation of data obtained in the addiction liability program has also been discussed in previous project descriptions.

7. Location of Project

Work will be carried out at the NIMH Addiction Research Center, PHS Hospital, Lexington, Kentucky. This institution provides the two necessary facilities for the type of work to be undertaken: (1) a pool of patients who will volunteer for experiments with drugs, and (2) strict environmental control which prevents the introduction of drugs other than those under study into the experimental situation.

8. Experimental Personnel

Work will be carried out under the direction of Harris Isbell,

M.D., Director, NIMH Addiction Research Center. This investigator has had thirteen years of experience in research in narcotic drug addiction and has published many papers in the field. He will be assisted by two other experienced physicians, Dr. H. F. Fraser and Dr. Abraham Wikler, both of whom have had extensive experience in research in addiction, with many publications. In addition to these medical personnel the part-time services of a biochemist and research psychologist will be made available. A special ward for the conduct of these studies is currently in operation.

9. Estimated Cost

The amount of money requested has been held to the same figure as was available in fiscal year 1957.

1. Personnel

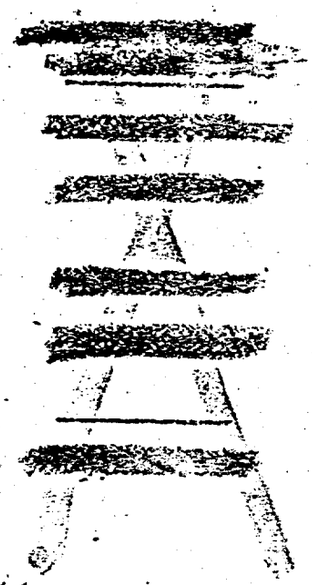
   6 Psychiatric Aides GS-5 ($4345. p.a.)
   1 Physical Science Aide GS-5

2. Reserve for Premium Pay
   (Night differential, Holiday, Overtime)

3. Travel

4. Miscellaneous Expense
   (Drugs, chemicals, glassware, photographic supplies, etc)

Total----------



This should be revised OK

Harris Isbell, M. D.
Director

HI:lw
18 February 1957

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